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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,290	07/22/2004	Ian Richard Catchpole	PG4744	1839

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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	**PAPER NUMBER**
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,290	CATCHPOLE, IAN RICHARD	
	Examiner	Art Unit	
	Satyendra K. Singh	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-20* is/are pending in the application.

4a) Of the above claim(s) *21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendments to the claims filed with the office on January 11th 2007 is duly acknowledged.

Claim 2 has been canceled by applicant's previous amendments to the claims.

Claims 21-24 (the invention of group II) remain withdrawn from further consideration.

Claims 1 and 3-20 (as currently amended) are examined on their merits in this office action, herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 3-20 (as amended) remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tuting & Albers [U] in view of Roser et al (US Patent 6,290,991 B1, [A]) and Volkin et al (WO 97/40839 A1, IDS).

Claims are generally directed to a DNA pharmaceutical agent dosage form having a dense core element (such as microbeads made of gold or tungsten), which is coated with a solid reservoir medium (such as a stabilizing polyol sugar or sugar glass) containing the DNA pharmaceutical agent that further comprises stabilizing agent that inhibit the degradative effects of free radicals. Specific limitations of the claims are:

Claims 1 and 7-12 are directed to a DNA pharmaceutical agent dosage form, having a **dense core element** coated with a solid reservoir medium containing the **DNA** pharmaceutical agent, further comprising a **stabilizing agent** that inhibits the degradative effects of free radicals; wherein the **solid reservoir medium** is an **amorphous polyol**; wherein the polyol is a **stabilizing polyol**; wherein the solid reservoir medium is a **sugar**; wherein the sugar is a member selected from the group consisting of lactose, glucose, raffinose and **trehalose**; wherein the solid reservoir medium is in the form of a glass; and wherein the solid reservoir medium is in the form of a **sugar glass**.

Claim 16 and 19-20 are directed to the DNA pharmaceutical agent dosage form wherein the DNA pharmaceutical agent is **a vaccine**; wherein the dense core element comprises **microbeads** of a mean particle diameter of **between 0.5 to 10 □m**; and wherein the microbeads are **gold or tungsten microbeads**.

Claims 17-18 are directed to the DNA pharmaceutical agent dosage form, wherein the solid reservoir medium further comprises a member selected from the group consisting of **vaccine adjuvant**, transfection facilitating agent, DNAase inhibitor, and a crystal poisoner; and wherein the vaccine adjuvant is a member selected from the group consisting of CpG, a synthetic imidazoquinoline, **a cytokine**, MPL, **QS21**, **QS7** and an oil in water emulsion.

Claims 3-6 are directed to the DNA pharmaceutical agent dosage form as claimed in claim 1, wherein the stabilizing agent is one or both of a **metal ion chelator** and a **free radical scavenger**; wherein the metal ion chelator is selected from the group consisting of chelators as recited in claim 4; wherein the free radical scavenger is selected from the group consisting of **ethanol, methionine and glutathione**; and wherein the stabilizing agent that inhibits the degradative effects of free radicals is a member selected from the group consisting of: phosphate buffered ethanol solution in combination with methionine or ethylenediamine tetraacetic acid (**EDTA**) and **Tris buffered EDTA** in combination with methionine or ethanol or a combination of **methionine and ethanol**.

Claims 13-15 are directed to the DNA pharmaceutical agent dosage form as claimed in claim 1, wherein the DNA pharmaceutical agent is **supercoiled plasmid DNA**; wherein the supercoiled DNA is **stabilized** such that after storage at 37 C for 4 weeks greater than **50% of the DNA remains in its supercoiled form**; and wherein the DNA is stabilized such that when released the ratio of monomer:dimer supercoiled form is within the range of 0.8:1.2.

Tuting & Albers [U] teach a DNA pharmaceutical agent dosage form having a **dense core element** (see discussion, supra) such as gold beads/particles/microcarriers of usually 0.6 to 3 μm in diameter (see pages 27, 30, 32, 34-36, and methods, in particular) coated with **plasmid DNA** encoding genes (for use as DNA immunization or **DNA vaccine**) using a Helios gene gun (commercially available from Bio-Rad, Richmond, CA, USA) for use in particle-mediated gene or nucleic acid transfer into dendritic cells. The DNA pharmaceutical agent dosage form taught by Tuting & Albers uses aqueous plasmid DNA formulations that are coated onto **gold beads/particles** by calcium

chloride precipitation method, and delivered by the gene gun (see Tuting & Albers, page 35, methods section 3.1.1, in particular).

However, a DNA pharmaceutical agent dosage form, having a dense core element coated with a **solid reservoir medium** containing the DNA pharmaceutical agent is not explicitly taught by Tuting & Albers [U].

Roser et al [A] teach a solid dose delivery vehicle (in the form of microbeads / microspheres / microfibers having particle sizes such as 0.1 to 10 μm, which varies depending on the use or route of administration; see Roser et al, abstract, summary of the invention, Figs. 1-4, columns 13-14, examples 1-7, and claims, in particular) for ballistic administration of a bioactive materials (such as DNA, proteins, and therapeutic and prophylactic agents; see Roser et al, columns 5-6, in particular) to subcutaneous and intradermal tissue, the delivery vehicle/particles being sized and shaped for penetrating the epidermis. The delivery vehicle further comprises a stabilizing **polyol glass** (such as an amorphous, stabilizing, glass forming and biodegradable polyols made of carbohydrates including sugars such as **trehalose**; see Roser et al, summary of the invention, column 3-4, column 6, last paragraph, and column 7, column 11, first paragraph, in particular) loaded with the bioactive material, and capable of slowly releasing the bioactive material *in situ* (see Roser et al, columns 12-13, in particular). Roser et al [A] also teach the solid dose delivery vehicle comprising immunogenic compositions further containing biological modifiers such as cytokines, interleukins, enzymes, and effective amounts of vaccine adjuvant including saponin derivatives (claimed adjuvants such as QS21 and QS7 in claim

18 are also saponins) (see Roser et al, column 6, third paragraph, in particular). Roser et al further disclose that the factors to be considered (including the immunogenicity, use of immunostimulating complexes, covalent attachment to an adjuvant or carrier protein, route of administration, and number of immunizing doses) for optimal vaccine development using such DNA pharmaceutical agent are well known in the art, and "it is well within the skill of immunologists to make such determinations without undue experimentation" (see Roser et al, column 6, 3rd paragraph, in particular).

However, the DNA pharmaceutical agent dosage form further comprising a **stabilizing agent** that inhibits the degradative effects of free radicals (as recited in claims 3-6; see discussion supra), and the DNA pharmaceutical agent dosage form wherein the DNA pharmaceutical agent is supercoiled plasmid DNA (which is stabilized in a manner such as recited in claims 13-15), is not explicitly taught by the combined disclosures of Tuting & Albers [U] and Roser et al [A].

Volkin et al (WO 97/40839 A1; IDS) teach DNA vaccine formulations that stabilize the conformation of DNA pharmaceutical agents (see Volkin et al, abstract, summary of the invention, Figures, claims, pages 9-11 and examples therein) specifically the formulations of **nucleic acid vaccine products** and nucleic acid gene therapy products. Volkin et al teach various stabilizing agents such as metal ion chelators (such as **EDTA**, TRIS, and other **chelators** specifically recited in the instant claim 4; see Volkin et al, page 10, second paragraph, in particular) and non-reducing **free radical scavengers** (such as ethanol, **methionine**, glycerol, and dimethyl sulfoxide; see Volkin et al, page 11,

second paragraph, in particular) that inhibit the degradative effects of free radicals, and thus stabilize (in terms of longer storage period) and preserve the supercoil conformation of the plasmid DNA in order to be optimally effective as a **DNA vaccine** (see Volkin et al, pages 9-11 and page 12, third paragraph, and Figs. 10, 12-25, in particular). Volkin et al teach DNA pharmaceutical agent formulations wherein the stabilizing agent that inhibit the degradative effects of free radicals is phosphate buffered ethanol solution in combination with methionine or EDTA and Tris buffered EDTA in combination with methionine or ethanol or a combination of methionine and ethanol (see Volkin et al, tables 5, 9, 10, 13, and Figs. 14, 20-24, 28, in particular); wherein the **supercoiled plasmid DNA is stabilized** such that after storage at 37^0 C for 4 weeks greater than 50% of the DNA remains in its supercoiled form; wherein the DNA is stabilized such that when released the ratio of monomer : dimmer supercoiled form is within the range of 0.8-1.2 as evidenced by the method of detection used to detect supercoiled plasmid DNA and the stability data disclosed by the referenced invention (see Volkin et al, Tables 5, 9, 10, 13 and data figures 14, 20-24, 28, and examples 5, 11-16, 18, in particular).

It would have been obvious to a person of ordinary skill in the art at the time this invention was made to modify the DNA pharmaceutical agent dosage form having a dense core element (i.e. plasmid DNA coated gold beads/particles) such that it is coated with a solid reservoir medium (such as stabilizing, solid, amorphous, biodegradable, polyol sugar glass, made of carbohydrates such as trehalose) containing the DNA pharmaceutical agent as explicitly taught by Roser

et al [A]; and also such that it further comprises a stabilizing agent that inhibits the degradative effects of free radicals (such as metal ion chelator, EDTA and/or free radical scavenger, methionine or ethanol) as explicitly taught by Volkin et al (IDS) in order to preserve the supercoiled structure of the plasmid DNA and to increase the ability to store the pharmaceutical DNA agent for longer period of time at 37 ^{0}C.

The person of ordinary skill in the art would have been motivated to make such modifications in the DNA pharmaceutical agent dosage form of Tuting & Albers because:

(1) Roser et al [A] explicitly disclose the benefits of using a solid dose delivery vehicle for ballistic administration of a biological/bioactive material including nucleic acids or DNA, proteins, therapeutic and prophylactic agents or compositions to skin tissue, which comprises a stabilizing, amorphous, biodegradable, polyol glass made of sugars such as trehalose, loaded with the bioactive materials and capable of releasing the bioactive material *in situ* (see Roser et al, abstract, summary of the invention, and column 3, first and second paragraph, in particular). Roser et al disclose the existing problems in the powder formulations in the prior art that use dense core elements such as gold or tungsten microparticles coated with DNA agent as delivery vehicles for ballistic administrations (see Roser et al, column 2, last paragraph, in particular) that were largely unsuitable because of the irregularities in the particle size and shape of the available powders, and provide a simple and economical solution and associated advantages of using solid dose drug delivery vehicles of defined

size, shape and density in order to ensure uniform distribution, minimize tissue damage, reduced damage to the delivery vehicle/particles, and facilitating the long-term storage of the loaded delivery vehicle, thus resulting in an increased efficacy in drug delivery to the target tissue (see Roser et al, column 3, second paragraph, in particular); and

(2) Volkin et al (IDS) disclose the benefits and DNA vaccine formulations that use stabilizing agent such as a metal ion chelator (EDTA, TRIS, as recited in claim 4) and/or a non-reducing free radical scavenger (ethanol or methionine) in order to inhibit the degradative effects of free radicals, and therefore, stabilize the supercoiled conformation of plasmid DNA in the DNA pharmaceutical agent (see Volkin et al, abstract, summary of the invention, and pages 9-11, in particular) and thus provide efficient, long-term storage formulations that are useful as DNA vaccines. Volkin et al provide a detailed disclosure for the effects of various factors influencing the stability of plasmid DNA (including types of metal ion chelators, various buffers with or without chelator, pH, temperature, light exposure, and ionic strength) and explicitly suggest the advantages of using metal ion chelator such as EDTA, and/or free radical scavenger such as ethanol and methionine as part of DNA formulations that are useful for stabilization of the supercolied conformation of DNA pharmaceutical agent (see discussion, supra).

One of ordinary skill in the art would have had a reasonable expectation of success when modifying the DNA pharmaceutical dosage form (i.e. DNA coated gold particles or microcarriers) of Tuting & Albers by the combined teachings of Roser et al and Volkin et al, because they provide explicit disclosures about (1)

the use of stabilizing, amorphous, biodegradable, polyol glass made of sugars such as trehalose, loaded with the bioactive materials and capable of releasing the bioactive material *in situ;* and (2) the use of a stabilizing agent such as a metal ion chelator (EDTA, TRIS, as recited in claim 4) and/or a non-reducing free radical scavenger (ethanol or methionine) that inhibit the degradative effects of free radicals, in order to preserve the supercoiled structure of the plasmid DNA and also to increase the ability to store the pharmaceutical DNA agent for longer period of time at 37 ^{0}C. Given the benefits accrued by adapting the modifications taught by both, Roser et al and Volkin et al for improving and stabilizing the DNA pharmaceutical agent dosage form of Tuting & Albers, one of ordinary skill in art would be motivated to make such modifications in the solid dose delivery vehicle (for DNA pharmaceutical agent formulations) to optimize the efficiency of DNA vaccine delivery using various administration techniques (such as ballistic delivery to skin tissue) that use solid DNA pharmaceutical agent dosage forms such as claimed in the instant invention.

As per MPEP 2144.06, It is well known that it is prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. In re Pinten, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); In re Susi, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made.

Response to Applicant's Arguments

Applicant's arguments filed with the office on January 11th 2007 (as they pertain to the prior art rejections of record) have been fully considered but they are not persuasive for the reasons of record as follows:

> Claims are generally directed to a DNA pharmaceutical agent dosage form (i.e. a solid dose delivery vehicle for DNA pharmaceuticals) comprising a dense core element coated with reservoir medium containing the DNA pharmaceutical agent, further comprising a stabilizing agent that inhibits the degradative effects of free radicals.

The prior art references (Tuting & Albers, in view of Roser et al and Volkin et al) relied upon by the examiner in the obviousness rejection under 35 U.S.C. 103(a) (as discussed in the previous office action) teach a DNA pharmaceutical agent dosage form (suitable for ballistic delivery; see Roser et al, abstract, and column 12, last paragraph, in particular) that has a dense core element, and that can be modified to have a coating of stabilizing polyol (such as trehalose sugar glass), a stabilizing agent to prevent from the damage caused by free radicals, and which can also include bioactive materials (such as therapeutic, diagnostic or prophylactic substances).

Applicant's argument (see remarks, page 6, under 103 obviousness) that Tuting & Albers do not disclose the use of metal ion chelators, such as EDTA for stabilizing the DNA being coated on the gold particles, is acknowledged and fully considered. However, the prior art rejection under 35 USC 103(a) as set forth in the previous office action (Tuting & Albers, in view of Roser et al and Volkin et al; see page 7 and 9, in particular) makes it clear that such chelating agents have been used for stabilization of DNA pharmaceuticals (used for vaccine formulations; see disclosure of Volkin et al), and therefore one of ordinary skill in

the art would have been motivated to modify the composition of Tuting & Albers (in view of Volkin et al) when preparing such DNA pharmaceutical dosage forms.

Contrary to the applicant's urging that the examiner's remarks on page 9 (as quoted by applicants), and the disclosure of Roser et al "teaches away" (see applicant's remarks, page 7, 3rd paragraph, in particular) from the use of gold beads as a delivery method, and therefore an artisan of ordinary skill would not be motivated to combine the teachings of Roser et al to modify the delivery vehicle as taught by Tuting & Albers, the teachings of Roser et al in fact, provide the basis for modifying the delivery vehicle of Tuting & Albers using polyol sugars (as a solid reservoir medium; such as trehalose or sugar glass, as taught by Roser et al) so as to impart advantages such as uniform distribution, stability during storage, minimizing tissue damage, etc, as clearly discussed in the body of the rejection (see previous office action, page 9, first paragraph, in particular; and also see disclosure of Roser et al, column 5, 1st paragraph, in particular).

Since, the cited prior art references disclose all the limitations for a DNA pharmaceutical dosage form (in the form of a solid dose delivery vehicle having a dense core element, as recited in the instant invention), applicant's assertion that "the three references are incompatible to each other with the regard to the presently claimed invention" (see applicant's remarks, page 8, 1st paragraph), is not found to be persuasive, and therefore the obviousness rejection of record is properly maintained.

Conclusion

NO claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyendra K. Singh whose telephone number is 571-272-8790. The examiner can normally be reached on 9-5MF (alternate Fridays OFF).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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